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## Ambient Air Pollution and Stroke

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### Background

Stroke is a leading cause of death in the US<sup>1</sup> and worldwide ([www.who.int](http://www.who.int)) and may lead to considerable neurological sequelae including aphasia, paraplegia and dementia. The estimated health care costs of stroke in the US exceed \$36 billion per year<sup>1</sup>. A large body of evidence supports the association between ambient air pollution exposure and increased cardiovascular mortality and morbidity<sup>2</sup>, but only recently have several studies specifically demonstrated an association with increased stroke risk.

Major sources of air pollution include traffic, power plants and in developing countries, biomass combustion. Both particles and gases are emitted through combustion. Particulate matter with aerodynamic diameter <10 µm (PM<sub>10</sub>) include ultrafine particles (PM<sub>1.0</sub>), fine particles (PM<sub>2.5</sub>) and coarse particles (PM<sub>10–2.5</sub>). Ultrafine particles are emitted in fresh exhaust and coalesce into PM<sub>2.5</sub> within a short time frame. PM<sub>2.5</sub> includes both local sources from traffic emissions and domestic heating and regional sources from power plants, biogenic emissions and traffic whereas coarse particles are a heterogenous mixture that include road dust, endotoxins, and suspended crustal matter. Carbon monoxide (CO), nitrogen dioxide (NO<sub>2</sub>), nitrogen oxides (NO<sub>x</sub>), sulfur dioxide (SO<sub>2</sub>) and ground-level ozone (O<sub>3</sub>) are gaseous pollutants emitted as a result of combustion processes. CO is mainly attributed to mobile sources in urban environments and NO<sub>2</sub> and NO<sub>x</sub> are rapidly formed in emissions from combustion sources such as traffic and power plants. The main source of SO<sub>2</sub> is from fossil fuel power plants. Ground-level O<sub>3</sub> is formed as a result of atmospheric reactions of NO<sub>2</sub> with hydrocarbons in the presence of sunlight and is a major constituent of photochemical smog. Several of the mentioned pollutants are regulated based on evidence of adverse health effects<sup>3</sup>. Possible mechanistic pathways including induction of oxidative stress, inflammation, atherosclerosis and autonomic dysregulation have been outlined in detail<sup>2–4</sup> and are beyond the scope of the current review.

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#### Online supplemental tables

Table I. Studies of Short-term Air Pollution Exposure and Stroke Mortality: Detailed estimates.

Table II. Studies of Short-term Air Pollution Exposure and Hospitalization for Stroke: Detailed estimates.

**Disclosures:** None

This review aims to assess the current evidence regarding the association of air pollution exposure with incidence of ischemic and hemorrhagic stroke considering long-term and short-term exposure to ambient pollutants.

## Long-Term Air Pollution Exposure

Most studies of long-term exposure to air pollution and stroke outcomes have used estimates of exposure at residential address in months to years as a proxy for long-term accumulated individual exposure. Exposure has then been assessed using residential distance to major roadways, measurements from closest available fixed monitor or advanced modeling of pollutants combining fixed monitoring measurements with land-use data, emissions databases, traffic density counts and meteorology incorporated into geographical information systems (GIS). These GIS models can also include population-based data such as average income level and average smoking prevalence.

### Long-term air pollution exposure and stroke mortality

Studies considering long-term exposure to air pollution and stroke mortality have reported that living in areas with higher ambient pollution is associated with higher risk of stroke mortality (Table 1). Studies from the UK<sup>5, 6</sup> and northwest Florida<sup>7</sup> containing large administrative databases with cause of death, residence, sex and area-based data such as socioeconomic status, urbanization, smoking prevalence and greenness. Living near a main road<sup>5</sup>, traffic sources<sup>7</sup>, point sources of emissions<sup>7</sup> or higher modeled exposure to PM<sub>10</sub>, CO and NO<sub>x</sub><sup>6</sup> were all associated with stroke mortality. Several cohort studies have also studied the association between long-term exposure to air pollution and stroke mortality<sup>8–13</sup>. These studies have more detailed individual-level data that improves the ability to adjust for potential confounders that may influence the place of residence and the risk of stroke mortality. Strongest associations were reported in the prospective Womens' Health Initiative cohort<sup>11</sup> that included well-validated outcome assessment. In the Californian residents of the American Cancer Society cohort study<sup>9</sup>, associations were reported for NO<sub>2</sub> and any stroke mortality and borderline significant associations for PM<sub>2.5</sub>. In the California Teachers Study<sup>10</sup>, however, higher long-term PM<sub>10</sub> and PM<sub>2.5</sub> exposure were not associated with cerebrovascular mortality. In 232 rural districts of Japan<sup>12</sup> including 250 stroke deaths, higher long-term PM<sub>10</sub> exposure was not associated with stroke mortality. Specific characterization of stroke into types and subtypes was available in two studies, in Shizuoka, Japan<sup>13</sup> and in Denmark<sup>8</sup>. Yorifuji et al<sup>13</sup> reported associations between NO<sub>2</sub> and mortality from ischemic stroke and intracerebral hemorrhage but not subarachnoid hemorrhage. Andersen et al<sup>8</sup> reported borderline significant associations between long-term NO<sub>2</sub> exposure and ischemic stroke but not for hemorrhagic strokes and did not further subtype hemorrhagic strokes.

### Long-term air pollution exposure and hospitalization for stroke

In studies of long-term exposure to air pollution and hospitalization for stroke, higher exposure at home addresses was also associated with higher risk of admission for stroke in some studies, but results were less consistent than for stroke mortality (Table 2). Most commonly reported pollutants included long-term exposure to PM<sub>10</sub><sup>6, 10, 14, 15</sup>,

PM<sub>2.5</sub><sup>10, 11, 16</sup> and NO<sub>x</sub><sup>6, 17, 18</sup> or NO<sub>2</sub><sup>8, 14, 15, 19, 20</sup>. Many of the cohort studies reported positive associations<sup>8, 10, 11, 14, 21</sup> whereas ecological studies<sup>6, 15, 19</sup> and case-control studies<sup>17, 18, 21</sup> showed mixed results. In a random-effects meta-analysis of 11 European cohorts<sup>16</sup>, long-term PM<sub>2.5</sub> was associated more strongly with stroke in subjects older than 60 years old, never-smokers and among subjects with exposure levels less than 25 µg/m<sup>3</sup> (current annual mean air quality standard in Europe). Studies that compared long-term air pollution exposure and hospital admissions according to specific stroke type reported positive associations for NO<sub>2</sub>, CO and traffic density and admissions for both ischemic and hemorrhagic stroke<sup>19</sup> in Edmonton, Canada whereas NO<sub>2</sub><sup>8, 20</sup> in Denmark or NO<sub>x</sub><sup>15</sup> in London, UK demonstrated associations consistent with ischemic stroke but not hemorrhagic stroke. Two studies from Scania, Sweden<sup>17, 18</sup> only including hospital admissions for ischemic stroke observed associations between higher long-term exposure to NO<sub>x</sub> and higher risk of hospital admission for ischemic stroke in participants with diabetes but found no association in the overall population, in smokers, or in participants with hypertension or atrial fibrillation. A recent population-based cohort study in Denmark studying long-term NO<sub>2</sub> and traffic noise exposure and stroke incidence reported positive associations for ischemic stroke in separate analyses for both noise and NO<sub>2</sub> but in combined analyses NO<sub>2</sub> was only associated with fatal ischemic strokes<sup>20</sup>.

## Short-term Air Pollution Exposure

Day to day differences in air pollution exposure in the days preceding stroke are used to study possible triggering effects of air pollution on stroke. In time-series analyses, daily counts of stroke deaths or admissions are compared with air pollution levels on the same day or preceding days in a study region. In case-crossover analyses exposure levels preceding stroke mortality or hospitalization in an individual are contrasted with control periods within the same calendar month within each individual controlling for season and day of week and perfectly matching time-invariant patient characteristics by design.

A number of studies have investigated associations between short-term exposure to air pollutants including PM<sub>10</sub>, PM<sub>2.5</sub>, CO, NO<sub>2</sub>, SO<sub>2</sub> and O<sub>3</sub> and stroke mortality or hospitalizations for stroke in many cities in North America, Europe and East Asia. Mean levels of pollutants varied considerably between study locations from low polluted cities like Dijon, France (daily mean PM<sub>10</sub> 20 µg/m<sup>3</sup>) to highly polluted cities like Wuhan, China (daily mean PM<sub>10</sub> 119 µg/m<sup>3</sup>).

## Short-term air pollution exposure and stroke mortality

A majority of studies investigating short-term exposure to air pollution and stroke mortality have been time-series studies<sup>22–36</sup>, the remainder used case-crossover design<sup>37–41</sup>. A qualitative summary of the studies is provided in Table 3 (for detailed estimates please see Table I <http://stroke.ahajournals.org>). Most studies do not differentiate between ischemic and hemorrhagic stroke mortality. Several studies reported associations between short-term exposure to particle matter, including several size fractions, or gases and any stroke mortality. Only a few studies further characterized stroke into ischemic and hemorrhagic stroke mortality<sup>24, 33–35, 38</sup>. Short-term exposure to particulate matter and gases were associated with both ischemic stroke and hemorrhagic stroke. In Tokyo<sup>34</sup> the risk increase

for subarachnoid hemorrhage mortality per 10  $\mu\text{g}/\text{m}^3$   $\text{PM}_{2.5}$  or  $\text{NO}_2$  was roughly double the risk increase for ischemic or intracerebral hemorrhage mortality. It is possible that these hemorrhages may have more precise temporal relationship between air pollution exposure and the timing of stroke onset leading to less exposure misclassification and more precise estimation of the association<sup>42</sup>. Stronger associations between short-term air pollution exposure and stroke mortality were observed in elderly<sup>25, 30</sup>, women<sup>25</sup> and individuals with a history of diabetes<sup>41</sup> or cardiac disease<sup>38</sup> in some but not all studies.

### Short-term air pollution exposure and hospitalization for stroke

Studies of short-term air pollution exposure and hospitalization for any stroke have reported mixed results<sup>43–63</sup>. However, in contrast to studies investigating short-term exposure to air pollution and stroke mortality that typically use death certificate data, some studies of associations with hospital admissions for stroke have had more data on stroke type. These studies have reported associations between  $\text{PM}_{10}$ <sup>45, 46, 64, 65</sup>,  $\text{PM}_{2.5}$ <sup>66–68</sup>, black carbon<sup>68</sup>,  $\text{CO}$ <sup>51, 58, 64</sup>,  $\text{NO}_2$ <sup>43, 58, 64, 68</sup>, and  $\text{O}_3$ <sup>62, 69, 70</sup> and ischemic stroke (Table 4, for detailed estimates please see Table II <http://stroke.ahajournals.org>). A majority did not observe associations between air pollutants and hemorrhagic stroke<sup>45, 58, 62, 65, 69</sup> with a few exceptions<sup>56, 57, 63, 64, 71</sup> including one study that specifically investigated days in Taiwan polluted by Asian dust storms originating from the Gobi desert<sup>63</sup>. Of the studies with specific data on subtype of ischemic stroke,  $\text{PM}_{10}$ ,  $\text{PM}_{2.5}$  and  $\text{O}_3$  were associated with strokes characterized as large-artery atherosclerotic strokes, small-vessel occlusions, lacunar strokes or TIAs rather than cardioembolic strokes<sup>46, 67–69</sup>. Stronger associations were reported for recurrent ischemic strokes or history of stroke<sup>58, 70</sup>, in individuals with diabetes or on diabetes medication<sup>67, 70</sup>, and with one or more cardiovascular risk factors<sup>69, 70</sup>. A few studies reported stronger associations between  $\text{O}_3$  and ischemic stroke in men than women<sup>62, 69, 72</sup>. Air pollution on warm days was more strongly associated with both hemorrhagic and ischemic stroke in Taiwan<sup>64</sup>. Associations between air pollution and ischemic stroke were stronger in the warm season in Edmonton, Canada<sup>58</sup> and Dijon, France<sup>70</sup> in contrast to Wuhan<sup>61</sup> where associations were stronger in the cold season. Differences may reflect better exposure classification due to time spent outdoors in climates like Edmonton, Canada but may also be due to seasonal interactions between pollutants.

### Summary

The current evidence suggests exposure to higher levels of air pollutants related to combustion increases the risk of stroke. Studies of both long-term and short-term air pollution exposure suggest consistent evidence of increased risk of ischemic stroke and moderately consistent evidence supporting an association with hemorrhagic stroke. A few studies exploring susceptible subgroups have indicated stronger associations in individuals with several cardiovascular risk factors, diabetes, previous stroke and of older age. A recently published meta-analysis focusing on short-term air pollution exposure and stroke incidence or mortality reported significant associations for  $\text{PM}_{2.5}$ ,  $\text{PM}_{10}$ ,  $\text{SO}_2$ ,  $\text{CO}$ ,  $\text{NO}_2$ , and  $\text{O}_3$  for stroke with stronger associations for ischemic stroke<sup>73</sup>.

Because much of the existing literature is based on linkage of administrative data, an important limitation of many available studies is limited ability to classify and validate

specific stroke outcomes. Ischemic stroke and hemorrhagic stroke and their subtypes have in the majority of studies been analyzed as a combined outcome despite the clear possibility that air pollution may affect underlying pathophysiologic pathways differently. Only some have separately analyzed ischemic stroke and hemorrhagic stroke and a handful have considered subtypes of ischemic stroke or hemorrhagic stroke. Similarly only a handful used thorough chart reviews and/or adjudicated the diagnosis and onset time of stroke. This highlights the need for high-quality validated diagnostic characterization of stroke outcome in studies of air pollution. In a study of short-term air pollution exposure and stroke specifically investigating the bias introduced through misclassification of time of event of stroke found that incorrect temporal classification caused up to 66% bias towards the null<sup>42</sup>. This may be especially relevant in mortality studies where the date of death from death certificates is used while not accounting for the time between stroke onset and death. In studies of long-term exposure to air pollution, the ability to investigate associations with stroke is dependent on the validity and resolution of the spatial exposure assessment and the adequate control for confounders related to both air pollution at place of residence and the risk of stroke, in particular socioeconomic factors.

There is growing evidence to suggest that both accumulated exposure to higher air pollution over a period of years and higher mean levels over a period of days increase the risk of stroke. In addition to improving temporal classification of exposure by validating stroke onset time, future research efforts should be directed to careful characterization of stroke subtype because air pollution may variably affect the different pathophysiological pathways. Air pollution exposure and increased risk of stroke may represent a considerable public health problem and regulations have improved air quality in many countries in Europe and the US, resulting in greater life expectancy<sup>74</sup>. Yet associations with stroke have been reported at levels in compliance with current standards<sup>16, 68</sup> highlighting the continued importance of effective regulation and monitoring in high income countries as well as extending efforts to address regulation in low and middle income countries where levels of air pollution and prevalence of stroke are on the rise.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

## Studies of Long-term Air Pollution Exposure and Stroke Mortality

Study	Location	Study Design	Stroke Outcome	Relative risk (95% Confidence Intervals)	Exposure
Maheswaran 2003 <sup>5</sup>	England and Wales	Ecological	Any stroke	1.05 (1.04, 1.07)	living within 200m of main road compared to 1000m
Maheswaran 2005 <sup>6</sup>	Sheffield, UK	Ecological	Any stroke	1.37 (1.19, 1.57) PM <sub>10</sub> 1.26 (1.10, 1.46) CO 1.33 (1.14, 1.56) NO <sub>x</sub>	highest to lowest quintile of modelled pollutant
Hu 2008 <sup>7</sup>	Florida, USA	Ecological	Any stroke	1.09 (1.03, 1.15)*	per 10,000 vehicles/day within census tract
Andersen 2012 <sup>8</sup>	Denmark	Cohort	Any stroke Ischemic Hemorrhagic	1.22 (1.00, 1.50) 1.46 (0.90, 2.39) 1.00 (0.76, 1.31)	per interquartile range increase (43%) in mean modeled NO <sub>2</sub> since 1971
Jerrett 2013 <sup>9</sup>	California, USA	Cohort	Any stroke	1.07 (0.99, 1.15) PM <sub>2.5</sub> 1.08 (1.02, 1.15) NO <sub>2</sub> 1.01 (0.92, 1.11) O <sub>3</sub>	per 5.3 µg/m <sup>3</sup> PM <sub>2.5</sub> per 4.12 ppb NO <sub>2</sub> per 24.2 ppb O <sub>3</sub>
Lipsitt 2011 <sup>10</sup>	California, USA	Cohort	Any stroke	0.99 (0.89, 1.09) PM <sub>10</sub> 1.16 (0.92, 1.46) PM <sub>2.5</sub>	per 10 µg/m <sup>3</sup> mean PM <sub>10</sub> 1996–2005, or mean PM <sub>2.5</sub> 1999–2005
Miller 2007 <sup>11</sup>	36 US cities	Cohort	Any stroke	1.83 (1.11, 3.00) PM <sub>2.5</sub>	annual mean in 2000 at closest monitor per 10 µg/m <sup>3</sup>
Ueda 2012 <sup>12</sup>	Japan	Cohort	Any stroke	0.86 (0.74, 1.01) PM <sub>10</sub>	per 10 µg/m <sup>3</sup> annual mean at closest monitor
Yorifuji 2013 <sup>13</sup>	Shizuoka, Japan	Cohort	Any stroke Ischemic Hemorrhagic	1.19 (1.06, 1.34) 1.20 (1.04, 1.39) 1.28 (1.05, 1.57)	per 10 µg/m <sup>3</sup> annual mean NO <sub>2</sub>

\* 95% Credible interval from a Bayesian analysis

Abbreviations: CO, Carbon monoxide. NO<sub>2</sub>, Nitrogen dioxide. NO<sub>x</sub>, Nitrogen oxides. O<sub>3</sub>, Ozone. PM<sub>10</sub>, Particles with aerodynamic diameter 10µm. PM<sub>2.5</sub>, Fine particles with aerodynamic diameter 2.5µm.

Table 2

## Studies of Long-term Air Pollution Exposure and Hospitalization for Stroke

Study	Location	Study Design	Stroke Outcome	Relative Risk (95% Confidence Intervals)	Exposure
Maheswaran 2005 <sup>6</sup>	Sheffield, UK	Ecological	Any stroke	1.13 (0.99, 1.29) PM <sub>10</sub> 1.11 (0.99, 1.25) CO 1.13 (1.04, 1.27) NO <sub>x</sub>	highest to lowest quintile of modelled pollutant
Andersen 2012 <sup>8</sup>	Denmark	Cohort	Any stroke Ischemic Hemorrhagic	1.05 (0.99, 1.11) 1.05 (0.95, 1.17) 0.93 (0.81, 1.07)	per interquartile range increase (43%) in mean modeled NO <sub>2</sub> since 1971
Lipsett 2011 <sup>10</sup>	California	Cohort	Any stroke	1.06 (1.00, 1.13) PM <sub>10</sub> 1.14 (0.99, 1.32) PM <sub>2.5</sub>	per 10 µg/m <sup>3</sup> annual mean pollutant at closest monitor
Miller 2007 <sup>11</sup>	36 US cities	Cohort	Any stroke	1.28 (1.01, 1.61) PM <sub>2.5</sub>	per 10 µg/m <sup>3</sup> mean of closest monitor during 2000
Maheswaran 2012 <sup>15</sup>	London, UK	Ecological	Ischemic Hemorrhagic	1.22 (0.77, 1.93) PM <sub>10</sub> 1.11 (0.93, 1.32) NO <sub>2</sub> 0.52 (0.20, 1.37) PM <sub>10</sub> 0.86 (0.60, 1.24) NO <sub>2</sub>	per 10 µg/m <sup>3</sup> of modelled pollutant exposure
Atkinson 2013 <sup>14</sup>	England	Cohort	Any stroke	0.98 (0.95, 1.01) PM <sub>10</sub> 0.99 (0.95, 1.03) NO <sub>2</sub> 1.02 (1.00, 1.05) SO <sub>2</sub> 1.00 (0.97, 1.04) O <sub>3</sub>	per 3.0 µg/m <sup>3</sup> PM <sub>10</sub> per 10.7 µg/m <sup>3</sup> NO <sub>2</sub> per 2.2 µg/m <sup>3</sup> SO <sub>2</sub> per 3.0 µg/m <sup>3</sup> O <sub>3</sub> modelled annual mean
Statfoggia 2014 <sup>16</sup>	11 cohorts, Europe	Cohort	Any stroke	1.19 (0.88, 1.62)	per 5 µg/m <sup>3</sup> annual mean PM <sub>2.5</sub>
Oudin 2009 <sup>17</sup>	Scania, Sweden	Case-control	Ischemic	0.95 (0.86, 1.06)	annual mean modelled NO <sub>x</sub> of 20–30 µg/m <sup>3</sup> vs <10 µg/m <sup>3</sup>
Oudin 2011 <sup>18</sup>	Scania, Sweden	Case-control	Ischemic	In diabetics: 2.0 (1.2, 3.4) high NO <sub>x</sub> 1.3 (1.1, 1.6) low NO <sub>x</sub>	Modelled annual NO <sub>x</sub> High NO <sub>x</sub> 25 µg/m <sup>3</sup> Low NO <sub>x</sub> <15 µg/m <sup>3</sup> Reference: non-diabetics with low NO <sub>x</sub>
Johnson 2010 <sup>19</sup>	Edmonton, Canada	Ecological	Any stroke Nonhemorrhagic Hemorrhagic	1.29 (1.16, 1.43) 1.36 (1.19, 1.56) 1.46 (1.19, 1.80)	highest (16.7–20.3 ppb) to lowest quintile (10.1–14.0 ppb) of NO <sub>2</sub> exposure
Sørensen 2014 <sup>20</sup>	Denmark	Cohort	Any stroke Ischemic Hemorrhagic	1.08 (1.01, 1.16) 1.11 (1.03, 1.20) 1.00 (0.80, 1.24)	per 10 µg/m <sup>3</sup> annual mean NO <sub>2</sub>

Study	Location	Study Design	Stroke Outcome	Relative Risk (95% Confidence Intervals)	Exposure
Johnson 2013 <sup>21</sup>	Edmonton, Canada	Case-control	Any stroke Ischemic TIA Hemorrhagic	1.01 (0.94, 1.08) 1.03 (0.94, 1.13) 0.95 (0.86, 1.05) 1.07 (0.92, 1.24)	per 5 ppb NO <sub>2</sub>

Abbreviations: CO, Carbon monoxide. NO<sub>2</sub>, Nitrogen dioxide. NO<sub>x</sub>, Nitrogen oxides. O<sub>3</sub>, Ozone. PM<sub>10</sub>, Particles with aerodynamic diameter 10µm. PM<sub>2.5</sub>, Fine particles with aerodynamic diameter 2.5µm. SO<sub>2</sub>, Sulfur dioxide.

Table 3

## Studies of Short-term Air Pollution Exposure and Stroke Mortality

Study	Location	Study Design	Stroke Outcome	Positive associations*	Null associations <sup>†</sup>
Chen 2013 <sup>22</sup>	8 Chinese cities	Time-series	Any stroke	PM <sub>10</sub> , NO <sub>2</sub> , SO <sub>2</sub>	
Hoek 2001 <sup>23</sup>	Netherlands	Time-series	Any stroke	Black smoke, CO, SO <sub>2</sub> , and O <sub>3</sub>	PM <sub>10</sub> and NO <sub>2</sub>
Hong 2002 <sup>24</sup>	Seoul, Korea	Time-series	Ischemic Hemorrhagic	TSP, CO, NO <sub>2</sub> , SO <sub>2</sub> , O <sub>3</sub>	CO, NO <sub>2</sub> , SO <sub>2</sub> , O <sub>3</sub>
Hong 2002 <sup>25</sup>	Seoul, Korea	Time-series	Any stroke	PM <sub>10</sub> , CO, NO <sub>2</sub> , SO <sub>2</sub> , O <sub>3</sub>	
Kan 2003 <sup>26</sup>	Shanghai, China	Time-series	Any stroke	PM <sub>10</sub> , NO <sub>2</sub>	SO <sub>2</sub>
Kettunen 2007 <sup>27</sup>	Helsinki, Finland	Time-series	Any stroke	PM <sub>2.5</sub> , CO in warm season	PM <sub>10</sub> , Coarse PM, PM <sub>0.1</sub> , NO <sub>2</sub> , O <sub>3</sub> in warm season. No associations in cold season.
Li 2011 <sup>28</sup>	Tianjin, Taiwan	Time-series	Any stroke	PM <sub>10</sub> on days with >20°C	PM <sub>10</sub> on days with < 20°C
Qian 2007 <sup>29</sup>	Wuhan, China	Time-series	Any stroke	PM <sub>10</sub>	
Qian 2007 <sup>30</sup>	Wuhan, China	Time-series	Any stroke	NO <sub>2</sub>	SO <sub>2</sub> , O <sub>3</sub>
Qian 2008 <sup>31</sup>	Wuhan, China	Time-series	Any stroke	PM <sub>10</sub> all days and NO <sub>2</sub> , SO <sub>2</sub> on normal temperature days	O <sub>3</sub> all days and NO <sub>2</sub> , SO <sub>2</sub> on high temperature days
Qian 2010 <sup>32</sup>	Wuhan, China	Time-series	Any stroke	NO <sub>2</sub> in spring, PM <sub>10</sub> , NO <sub>2</sub> , SO <sub>2</sub> in winter.	PM <sub>10</sub> and SO <sub>2</sub> in spring. All pollutants summer or fall.
Turin 2012 <sup>33</sup>	Takashima, Japan	Time-series	Any stroke Ischemic Hemorrhagic	NO <sub>2</sub>	Suspended PM, NO <sub>2</sub> , SO <sub>2</sub> , O <sub>3</sub> Suspended PM, SO <sub>2</sub> , O <sub>3</sub> Suspended PM, NO <sub>2</sub> , SO <sub>2</sub> , O <sub>3</sub>
Yorifuji 2011 <sup>34</sup>	Tokyo, Japan	Time-series	Any stroke Ischemic Hemorrhagic	PM <sub>2.5</sub> , NO <sub>2</sub> PM <sub>2.5</sub> , NO <sub>2</sub>	PM <sub>2.5</sub> , NO <sub>2</sub>
Yorifuji 2013 <sup>35</sup>	47 Japanese cities	Time-series	Any stroke Ischemic Hemorrhagic	PM <sub>10</sub>	PM <sub>10</sub> PM <sub>10</sub>
Zanobetti 2009 <sup>36</sup>	112 US cities	Time-series	Any stroke	PM <sub>2.5</sub> , PM <sub>10</sub> course	
Maynard 2007 <sup>37</sup>	Massachusetts, USA	Case-crossover	Any stroke	Black carbon	SO <sub>4</sub>
Qian 2013 <sup>38</sup>	Shanghai, China	Case-crossover	Any stroke Ischemic Hemorrhagic	PM <sub>10</sub> , NO <sub>2</sub> , SO <sub>2</sub> PM <sub>10</sub> , NO <sub>2</sub> , SO <sub>2</sub> NO <sub>2</sub> , SO <sub>2</sub>	PM <sub>10</sub>

Study	Location	Study Design	Stroke Outcome	Positive associations*	Null associations <sup>†</sup>
Ren 2010 <sup>39</sup>	Massachusetts, USA	Case-crossover	Any stroke	O <sub>3</sub>	
Zeka 2005 <sup>40</sup>	20 US cities	Case-crossover	Any stroke	PM <sub>10</sub>	
Zeka 2006 <sup>41</sup>	20 US cities	Case-crossover	Any stroke	PM <sub>10</sub> if pneumonia or 75 years old	PM <sub>10</sub> if no pneumonia or 75 years old

\* Positive associations with confidence intervals not including the null.

<sup>†</sup> Associations with confidence intervals including the null.

Abbreviations: CO, Carbon monoxide. NO<sub>2</sub>, Nitrogen dioxide. O<sub>3</sub>, Ozone. PM<sub>10</sub>, Particles with aerodynamic diameter 10µm. PM<sub>2.5</sub>, Fine particles with aerodynamic diameter 2.5µm. PM<sub>coarse</sub>, Coarse particles with aerodynamic diameter between 2.5 and 10 µm in aerodynamic diameter. PM<sub>0.1</sub>, Ultrafine particles with less than 0.1 µm aerodynamic diameter. SO<sub>2</sub>, Sulfur dioxide. SO<sub>4</sub>, Sulfate. TSP, Total suspended particles.

Table 4

## Studies of Short-term Exposure to Air Pollution and Hospital Admissions for Stroke

Study	Location	Study Design	Stroke Outcome	Positive associations*	Null Associations†
Ballester 2001 <sup>43</sup>	Valencia, Spain	Time-series	Any stroke	NO <sub>2</sub>	CO, SO <sub>2</sub> , O <sub>3</sub>
Burnett 1999 <sup>44</sup>	Toronto, Canada	Time-series	Any stroke		PM <sub>10</sub> , CO, NO <sub>2</sub> , O <sub>3</sub>
Chan 2006 <sup>45</sup>	Taipei, Taiwan	Time-series	Any stroke Ischemic Hemorrhagic	PM <sub>10</sub> , PM <sub>2.5</sub> , O <sub>3</sub>	CO, NO <sub>2</sub> , SO <sub>2</sub> PM <sub>10</sub> , PM <sub>2.5</sub> , CO, NO <sub>2</sub> , SO <sub>2</sub> , O <sub>3</sub> PM <sub>10</sub> , PM <sub>2.5</sub> , CO, NO <sub>2</sub> , SO <sub>2</sub> , O <sub>3</sub>
Correa 2012 <sup>46</sup>	Mantua, Italy	Case-crossover	Any stroke Ischemic	PM <sub>10</sub> PM <sub>10</sub> in all ischemic, large vessel, small vessel, and lacunar	PM <sub>10</sub> in cardioembolic, CO, NO <sub>2</sub> , SO <sub>2</sub> , O <sub>3</sub>
Jalaludin 2006 <sup>47</sup>	Sydney, Australia	Time-series	Any stroke		PM <sub>10</sub> , PM <sub>2.5</sub> , CO, NO <sub>2</sub> , SO <sub>2</sub> , O <sub>3</sub>
Larrieu 2007 <sup>48</sup>	8 French cities	Time-series	Any stroke		PM <sub>10</sub> , NO <sub>2</sub> , O <sub>3</sub>
Le Tertre 2002 <sup>49</sup>	8 European cities	Time-series	Any stroke		PM <sub>10</sub> , black smoke
Linn 2000 <sup>50</sup>	Los Angeles, USA	Time-series	Any stroke	CO, NO <sub>2</sub> in spring	PM <sub>10</sub> , O <sub>3</sub>
Moolgavkar 2000 <sup>51</sup>	Los Angeles, USA	Time-series	Any stroke	PM <sub>10</sub> , CO, NO <sub>2</sub> , SO <sub>2</sub>	PM <sub>2.5</sub>
Nascimento 2012 <sup>52</sup>	Sao Jose Campos, Brazil	Time-series	Any stroke	PM <sub>10</sub> , SO <sub>2</sub>	O <sub>3</sub>
Poloniecki 1997 <sup>53</sup>	London, UK	Time-series	Any stroke		Black smoke, CO, NO <sub>2</sub> , SO <sub>2</sub> , O <sub>3</sub>
Pönkä 1996 <sup>54</sup>	Helsinki, Finland	Time-series	Any stroke Ischemic	NO <sub>2</sub> Total suspended particles	
Sunyer 2003 <sup>55</sup>	7 European cities	Time-series	Any stroke		SO <sub>2</sub>
Tunin 2012 <sup>56</sup>	Takashima, Japan	Time-series	Any stroke Ischemic Hemorrhagic		PM <sub>10</sub> , NO <sub>2</sub> , SO <sub>2</sub> , O <sub>3</sub> PM <sub>10</sub> , NO <sub>2</sub> , SO <sub>2</sub> , O <sub>3</sub> PM <sub>10</sub> , NO <sub>2</sub> , O <sub>3</sub>
Villeneuve 2006 <sup>57</sup>	Edmonton, Canada	Case-crossover	Any stroke Ischemic TIA Hemorrhagic	PM <sub>2.5</sub> SO <sub>2</sub>	PM <sub>10</sub> , PM <sub>2.5</sub> , CO, NO <sub>2</sub> , SO <sub>2</sub> , O <sub>3</sub> CO, NO <sub>2</sub> , SO <sub>2</sub> , O <sub>3</sub> PM <sub>10</sub> , PM <sub>2.5</sub> , CO, NO <sub>2</sub> , SO <sub>2</sub> , O <sub>3</sub>

Study	Location	Study Design	Stroke Outcome	Positive associations*	Null Associations <sup>†</sup>
Villeneuve 2012 <sup>58</sup>	Edmonton, Canada	Case-crossover	Any stroke Ischemic Hemorrhagic	CO in warm season CO, NO <sub>2</sub> , O <sub>3</sub> in warm season	PM <sub>10</sub> , PM <sub>2.5</sub> , CO, NO <sub>2</sub> , O <sub>3</sub> PM <sub>2.5</sub> , NO <sub>2</sub> , SO <sub>2</sub> , O <sub>3</sub> , CO all year. PM <sub>2.5</sub> , NO <sub>2</sub> , SO <sub>2</sub> , O <sub>3</sub> , CO all year. PM <sub>2.5</sub> , CO, NO <sub>2</sub> , SO <sub>2</sub> , O <sub>3</sub>
Wong 1999 <sup>59</sup>	Hong Kong, China	Time-series	Any stroke		PM <sub>10</sub> , NO <sub>2</sub> , SO <sub>2</sub> , O <sub>3</sub>
Wordley 1997 <sup>60</sup>	Birmingham, UK	Time-series	Any stroke	PM <sub>10</sub>	
Xiang 2013 <sup>61</sup>	Wuhan, China	Case-crossover	Any stroke	PM <sub>10</sub> , NO <sub>2</sub> in cold season	PM <sub>10</sub> , NO <sub>2</sub> , SO <sub>2</sub> all year and in subtypes. PM <sub>10</sub> , NO <sub>2</sub> in warm season.
Xu 2013 <sup>62</sup>	Allgheny, USA	Case-crossover	Any stroke Ischemic Hemorrhagic	O <sub>3</sub> O <sub>3</sub>	O <sub>3</sub>
Yang 2005 <sup>63</sup>	Taipei, Taiwan	Time-series	Any stroke Ischemic TIA Hemorrhagic	Asian dust and intracerebral Asian dust Asian dust and subarachnoidal	Asian dust Asian dust Asian dust and subarachnoidal
Tsai 2003 <sup>64</sup>	Kaoshiung, Taiwan	Case-crossover	Ischemic Hemorrhagic	PM <sub>10</sub> , NO <sub>2</sub> , SO <sub>2</sub> , O <sub>3</sub> warm days, CO all days PM <sub>10</sub> , CO, NO <sub>2</sub> , O <sub>3</sub> warm days	PM <sub>10</sub> , NO <sub>2</sub> , SO <sub>2</sub> , O <sub>3</sub> cool days SO <sub>2</sub> warm days, All pollutants cool days
Wellenius 2005 <sup>65</sup>	9 US cities	Case-crossover	Ischemic Hemorrhagic	PM <sub>10</sub> , CO, NO <sub>2</sub> , SO <sub>2</sub>	PM <sub>10</sub> , CO, NO <sub>2</sub> , SO <sub>2</sub>
Lisabeth 2008 <sup>66</sup>	Corpus Christi, USA	Time-series	Ischemic	PM <sub>2.5</sub>	O <sub>3</sub>
O'Donnell 2011 <sup>67</sup>	8 Canadian cities	Case-crossover	Ischemic	PM <sub>2.5</sub> in diabetics and non-cardioembolic	PM <sub>2.5</sub> in ischemic strokes overall
Wellenius 2012 <sup>68</sup>	Boston, USA	Case-crossover	Ischemic	PM <sub>2.5</sub> , black carbon, NO <sub>2</sub> , PM <sub>2.5</sub> large and small vessel stroke	CO, SO <sub>4</sub> , O <sub>3</sub> , PM <sub>2.5</sub> cardioembolic stroke
Henrotin 2007 <sup>69</sup>	Dijon, France	Case-crossover	Ischemic Hemorrhagic	O <sub>3</sub> in all ischemic, large vessel, and TIA	PM <sub>10</sub> , CO, NO <sub>2</sub> , SO <sub>2</sub> PM <sub>10</sub> , CO, NO <sub>2</sub> , SO <sub>2</sub> , O <sub>3</sub>
Henrotin 2010 <sup>70</sup>	Dijon, France	Case-crossover	Ischemic	O <sub>3</sub> in recurrent stroke	O <sub>3</sub> in recurrent stroke
Yamazaki 2007 <sup>71</sup>	Japan	Case-crossover	Ischemic	PM <sub>7</sub> , 2h before intracerebral hemorrhage	PM <sub>7</sub> , NO <sub>2</sub> , O <sub>3</sub> in 24h averages
Bedada 2012 <sup>72</sup>	UK	Case-crossover	Minor stroke	NO	CO, NO <sub>2</sub> , SO <sub>2</sub> , O <sub>3</sub>

\* Positive associations with confidence intervals not including the null.



<sup>†</sup>Associations with confidence interval including the null.

Abbreviations: BC, Black carbon. BS, Black smoke. CI, Confidence intervals. CO, Carbon monoxide. H, hour. Max, Daily maximum. NO, Nitric oxide. NO<sub>2</sub>, Nitrogen dioxide. NS, Non-significant associations but estimates not provided in publication. O<sub>3</sub>, Ozone. PM<sub>10</sub>, Particles with aerodynamic diameter 10µm. PM<sub>2.5</sub>, Fine particles with aerodynamic diameter 2.5µm. PM<sub>coarse</sub>, Coarse particles with aerodynamic diameter between 2.5 and 10 µm in aerodynamic diameter. PM<sub>0.1</sub>, Ultrafine particles with less than 0.1 µm aerodynamic diameter. SO<sub>2</sub>, Sulfur dioxide. SO<sub>4</sub>, Sulfate. TSP, Total suspended particles.